FDA PMA P110033 Executive Summary
General and Plastic Surgery Devices Panel Advisory Committee

Allergan
Juvéderm Voluma XC
May 2, 2013
Hilton Washington DC North
Gaithersburg, MD 20877

FDA Executive Summary
Allergan's Juvéderm Voluma XC
P110033
May 2, 2013
Panel Meeting of General and Plastic Surgery Devices Panel

Introduction

This is the Executive Summary for Premarket Approval (PMA) application P110033 submitted by Allergan for the combination product named Juvéderm Voluma XC. Juvéderm Voluma XC is a viscous gel composed of cross-linked hyaluronic acid suspended in phosphate buffered saline with 0.3% Lidocaine. Juvéderm Voluma XC has been reviewed by the Plastic and Reconstructive Surgery Devices Branch in the Division of Surgical Devices in the Center for Devices and Radiological Health, Food and Drug Administration. This Executive Summary provides an overview of the information submitted by Allergan in P110033, the rationale for bringing P110033 to the Advisory Panel, and the FDA review team's summary of the product description, indications for use, pre-clinical testing, and clinical study.

Rationale for Bringing P110033 to the General and Plastic Surgery Devices Panel

The FDA review team is presenting P110033 to the General and Plastic Surgery Devices Panel for deliberation on the safety and effectiveness based upon the results of the Juvéderm Voluma XC clinical study. The product is being taken to Panel because dermal filler use in the midface is a significant new indication. The FDA review team seeks the Panel's input to determine whether the current data are sufficient to support an acceptable benefit/risk profile for the product's proposed indications for use. The FDA review team will provide a summary of the submission, and then provide an analysis of the data and remaining issues that will provide the basis for questions to the Advisory Panel at the Panel Meeting.

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I Background

Sponsor

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Establishment Registration No: 2024601

Manufacturer Information

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Route de Promery
Zone Artisanale de Pre-Mairy
Pringy, France 74370
Establishment Registration No: 3005113652

Indications for Use

JUVÉDERM VOLUMA™ XC is indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face.

Product Description

Juvéderm Voluma XC is a sterile, biodegradable, viscoelastic implant (dermal filler) containing crosslinked hyaluronic acid (HA). Juvéderm Voluma XC is formulated from a mixture of low and high molecular weight HA, and contains 0.3% lidocaine and phosphate buffered saline. The HA used for the Juvéderm Voluma XC formulation is produced by fermentation from Streptococcus equi bacteria, and is crosslinked with 1,4-butanediol diglycidyl ether (BDDE) to form a 3-dimensional HA gel. The HA gel is made primarily of crosslinked HA with some remaining lightly crosslinked and uncrosslinked HA. The product is packaged in 1 mL syringes and delivered with a 27G ½-inch and/or 25G 1-inch needle. Juvéderm Voluma XC is similar to previously approved Juvéderm products with the key major differences in Juvéderm Voluma XC being the inclusion of a mixture of low molecular weight and high molecular weight HA, midface indications, and higher injection volumes.

Principle of Operation

Implantation of crosslinked hyaluronic acid provides space-filling volume.

II Manufacturing Information

Materials

Lidocaine: The lidocaine hydrochloride specifications comply with the current EP Monograph 0227 for lidocaine HCl. The lidocaine Drug Master File was reviewed and found adequate by FDA's Center for Drug Evaluation and Research.

Hyaluronic Acid: Hyaluronic acid is supplied as a sodium salt. The sodium hyaluronate raw material specifications conform to the requirements of the EP Monograph 1472 for sodium hyaluronate. The hyaluronic acid Master File was reviewed and found adequate by FDA's Center for Devices and Radiological Health.

Sterilization

Filled syringes are sterilized using a validated moist heat process in a pressurized autoclave. The sterilization cycle is validated according to the FDA recognized ISO 17665-1 sterilization standard. The validated sterilization cycle provides a minimum Sterility Assurance Level (SAL) of 10^{-6}.

Stability

Stability data have been collected through 24 months at 25°C/60% relative humidity, through 12 months at 30°C/65% relative humidity, and through 6 months at 40°C/75% relative humidity. At each stability time point, the product was evaluated for conformance with all microbiological, physical, chemical, and lidocaine HCl potency specifications. As part of the stability studies, the lidocaine-related degradant MEGX was monitored and conformance with release specifications confirmed.

III Preclinical Testing

Verification of Product Specifications and Key Product Characterization Testing

Characterization of pH of Juvéderm Voluma XC: The pH was measured with a pH meter that was sensitive to hydrogen-ion activity and designed for viscoelastic materials. The results confirmed the pH is within the product release specifications.

Extrusion Force of Juvéderm Voluma XC: The extrusion force results confirmed that the extrusion force value for Juvéderm Voluma XC is within the product release specifications.

Colorimetric Analysis of Juvéderm Voluma XC: Colorimetric analysis of Juvéderm Voluma XC was performed to determine the hyaluronic acid concentration. The results confirmed the hyaluronic acid concentration in Juvéderm Voluma XC is within the product release specifications.

Determination of Lidocaine Concentration in Juvéderm Voluma XC: Lidocaine concentration was measured using high-pressure liquid chromatography (HPLC) analysis. The HPLC chromatographic conditions are identical to those of the European Pharmacopeia (EP) Monograph 0227 for lidocaine HCl. The results confirmed the lidocaine concentration is within the product release specifications.

Endotoxin Testing: Endotoxin levels were determined using the Limulus Amoebocyte Lysate (LAL) assay. This testing confirmed the levels of endotoxins in manufactured Juvéderm Voluma XC are within the product release specifications.

Diffusion of Lidocaine from Juvéderm Voluma XC: Diffusion of lidocaine was evaluated to ensure lidocaine is freely released from the gel matrix. The study was performed by dialyzing Juvéderm Voluma XC against deionized water, and measuring the time to reach an equilibrium concentration of lidocaine. The results demonstrated the lidocaine concentration decreased by approximately half in the first 1.5 hours, and then reached the plateau value of equilibrium concentration after approximately 20 hours, confirming that the lidocaine is freely released from the gel matrix.

Biocompatibility and Toxicology

The sponsor evaluated Juvéderm Voluma XC with *in vitro* and *in vivo* biocompatibility studies. The biocompatibility studies were performed in accordance with the Federal Good Laboratory Practices Regulations (21 CFR § 58), ISO10993 and FDA's Blue Book memorandum G95-1 "Use of ISO-10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing".

Material mediated pyrogenicity A material mediated pyrogenicity assay was performed for Juvéderm Voluma XC based on the current United States Pharmacopeia (USP) <151> to evaluate the potential for material mediated pyrogenicity. There was no indication of a pyrogenic response in this test.

Cytotoxicity: Juvéderm Voluma XC was evaluated for cytotoxicity using the agar overlay method per ISO 10993-5. There was no indication of cytotoxicity in this test.

Intracutaneous Reactivity: The potential for Juvéderm Voluma XC to cause irritation was assessed by the intracutaneous reactivity test per ISO 10993-10. The intracutaneous reactivity tests were performed using direct injection of 0.2 mL of undiluted Juvéderm Voluma XC. The first intracutaneous reactivity test was performed for 72 hours, as recommended in ISO 10993-10. Juvéderm Voluma XC failed to meet the acceptance criteria of this test. To further evaluate these findings, the sponsor repeated the intracutaneous reactivity test in a 14-day study using approved dermal filler product as controls, and evaluating 3 different lots of the Juvéderm Voluma XC. The repeat study demonstrated the irritation response elicited by Juvéderm Voluma XC was similar to approved dermal filler products, and that the irritation response declined to a minimal level in approximately 3 days.

Sensitization: A sensitization assay was performed per ISO 10993-10 to evaluate the potential for dermal sensitization. There was no indication of sensitization in this test.

Acute Systemic Toxicity: Juvéderm Voluma XC was tested per ISO 10993-11 to evaluate potential acute systemic toxicity. There was no evidence of acute systemic toxicity in this study.

Subchronic Toxicity: The potential of Juvéderm Voluma XC to cause subchronic toxicity was evaluated in a 13-week subchronic toxicity study per ISO 10993-6 and ISO 10993-10. There was no evidence of toxicity following intradermal injection of Juvéderm Voluma XC.

Muscle Implantation: Four and twelve week muscle implantation studies were conducted per ISO10993-6. There was no indication of irritation or inflammation in these studies.

Chronic Toxicity: A justification for not conducting a chronic toxicity study was provided, and included a consideration of the toxicity of the materials used to manufacture Juvéderm Voluma XC, the performance of the same materials in previously approved products, and the results of the biocompatibility testing conducted on Juvéderm Voluma XC.

Genotoxicity: The genotoxicity potential of Juvéderm Voluma XC and the residual cross-linking agent (BDDE) was assessed by a bacterial reverse mutation assay (Ames), mouse peripheral blood micronucleus assay, and a chromosomal aberration assay. This panel of genotoxicity testing meets the recommendations in ISO 10993-3, and the conditions of FDA's recognition of this standard. There was no evidence of genotoxicity or clastogenicity in any of the genotoxicity studies.

Carcinogenicity: The Juvéderm Voluma XC manufacturing process utilizes 1, 4-butanediol diglycidyl ether (BDDE) as a crosslinking agent, which is reported to be an animal carcinogen. FDA has previously conducted cancer risk assessments for products containing BDDE. In the current submission, the sponsor

provided an assessment of the potential cancer risk of residual BDDE from lifetime use of Juvéderm Voluma XC following the approach previously taken by FDA. The sponsor calculated the excess cancer risk assuming a maximum yearly dosage of Juvéderm Voluma XC of 20 mL. The excess cancer risks for Juvéderm Voluma XC range from 6.1×10^{-5} to 1.6×10^{-8} from lifetime exposure to residual BDDE based on a linear extrapolation method and a dose-response model. The calculated cancer risks for Juvéderm Voluma XC are in the same range of acceptable cancer risks as other previously approved dermal filler products.

Delivery System: The sponsor has conducted an adequate assessment of the syringe and needle delivery system per FDA's Blue Book memorandum G95-1 "Use of ISO-10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing".

FDA comments on Preclinical data

- The results of the preclinical testing demonstrate Juvéderm Voluma XC meets all product specifications.

- The sponsor provided a repeat intracutaneous irritation study to further evaluate the irritation response reported in the 3-day rabbit study. The results of the repeat irritation study demonstrated the irritation response was similar in magnitude and duration as approved dermal filler products, there was not significant lot-to-lot variability, and the irritation response declined to a minimal level in approximately 3 days. The macroscopic irritation evaluation was supplemented with a histological evaluation that did not report an adverse tissue response. Based on a review of these data, FDA concluded that no further irritation studies were warranted. The preclinical irritation studies suggest a short duration irritation response may be expected with clinical use of Juvéderm Voluma XC.

- FDA concluded a chronic toxicity study was unlikely to be informative based on a consideration of the toxicity risks posed by the materials used to manufacture Juvéderm Voluma XC, the acceptable performance of the same materials from the same suppliers in previously approved products, and absence of toxicity reported in the short and medium duration biocompatibility studies conducted on Juvéderm Voluma XC.

- FDA concluded the cancer risk assessment and residual BDDE purity specifications are adequate to mitigate the cancer risks of Juvéderm Voluma XC. This conclusion is further supported by the negative genotoxicity results obtained in an appropriate panel of genotoxicity studies conducted on Juvéderm Voluma XC.

- FDA concluded the preclinical testing provides a reasonable assurance the Juvéderm Voluma XC product will be biocompatible, and that all toxicity risks have been adequately mitigated.

IV Clinical Study

Clinical Study Design

15 investigational sites, each with a Treating Investigator (TI) and 2 Evaluating Investigators (EI), obtained Institutional Review Board approval. This clinical study report contains data obtained through 24 months for the treatment group, 18 months for the control group, and 30-days of follow up for the repeat treatment group.

Primary aim: The primary aim of this study was to evaluate the safety and effectiveness of Juvéderm Voluma XC for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face (Figure 1 and Table 1).

Figure 1 Mid-Face Treatment Sites

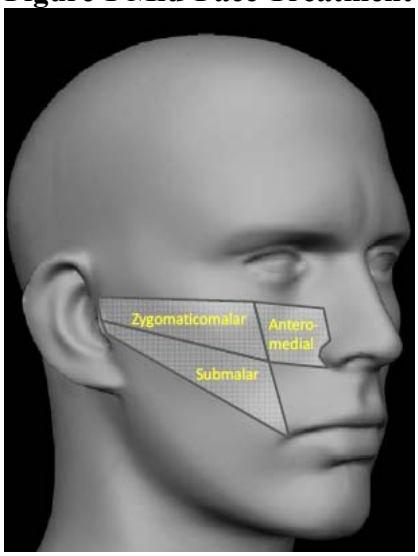


Table 1 Midface Treatment Sites

Treatment Site	Initial Treatment* (N = 270) % (n/N)	Touch-up Treatment* (N = 221) % (n/N)	Repeat Treatment (N = 125) % (n/N)
Zygomaticomalar Region	96.7% (261/270)	81.4% (180/221)	88.0% (110/125)
Right	95.6% (258/270)	74.2% (164/221)	85.6% (107/125)
Left	95.9% (259/270)	71.0% (157/221)	86.4% (108/125)
Anteromedial Cheek	95.6% (258/270)	77.8% (172/221)	84.0% (105/125)
Right	95.6% (258/270)	68.3% (151/221)	79.2% (99/125)
Left	95.2% (257/270)	72.9% (161/221)	82.4% (103/125)
Submalar Region	93.0% (251/270)	62.4% (138/221)	66.4% (83/125)
Right	91.9% (248/270)	55.2% (122/221)	63.2% (79/125)
Left	92.2% (249/270)	53.4% (118/221)	64.0% (80/125)

*N includes all treated mITT subjects.

Study Plan: The Juvéderm Voluma XC study is a multicenter, single-blinded, randomized, "no-treatment" control study consisting of up to 2 treatments with Juvéderm Voluma XC at the outset of the study (treatment group) compared to a no-treatment control. The no-treatment control group had their treatment delayed by at least 6 months. The first 2 subjects enrolled at each site were not randomized and were deemed run-in subjects (30 total run-in subjects), allowing each TI to have 2 treatment cases to gain experience with the injection characteristics of Juvéderm Voluma XC. Subjects were randomized to treatment or control using a 5.3:1 ratio. Treating Investigators performed study injections and were not blinded to subject randomization. Two blinded EI performed effectiveness assessments. Juvéderm Voluma XC was delivered via subcutaneous and/or supraperiosteal injection. Appropriate volume was determined by the TI, up to a maximum 12 syringes (12 mL). An optional repeat treatment was permitted after completion of the extended follow-up period (between 12 and 24 months), if subject's overall and individual treatment area MFVDS scores returned to baseline or worse. At Month 24 all subjects were offered an optional repeat treatment if they hadn't already received one; subjects were allowed a 3-month window to receive the optional retreatment.

Sample Size: Up to 345 subjects (30 run-in subjects, up to 240 treated subjects, and at least 45 control subjects) were planned. Analyzed subjects consisted of 30 run-ins, 235 treated subjects, and 47 control subjects. To achieve 85% power with a 2-sided exact binomial test at the 0.025 significance level, a minimum sample size of 36 was needed to demonstrate that ≥ 70% of subjects would be improved by ≥ 1 grade on the 6-point MFVDS at 6 months compared with the pre-treatment MFVDS assessment if the assumed responder rate in the treatment group was 90%. A sample size of 36 control subjects and 216 treated subjects provided > 99% power for a 2-sided 2-group Fisher's exact test at the 0.025 significance level to demonstrate statistical superiority of the treatment group over the control group if the assumed responder rate in the treatment group was 90% and in the control group was less than 40% at 6 months. Allowing for 20% attrition (drop-outs and protocol deviations) in the control group and 10% in the treatment group, the number of randomized subjects was set at 45 "no treatment" control subjects and 240 treated subjects. Each site treated up to 2 run-in subjects (up to 30 total). Thus, the overall planned enrollment was 315 subjects, which included 240 subjects in the treatment group, 45 subjects in the "no-treatment" control group, and 30 run-in subjects.

Primary Effectiveness: The primary effectiveness measure was the average of the 2 live blinded EIs assessments of the subject's overall mid-face volume deficit using the validated 6-point photometric Mid-Face Volume Deficit Scale (MFVDS) (Table 2). The primary effectiveness variable was the number of "responders" to Juvéderm Voluma XC. To be considered a "responder," the average of the blinded, independent EIs assessments of the subject's overall mid-face volume deficit at 6 months had to be improved (reduced) by ≥ 1 grade compared with the average of the EI pre-treatment assessments. Juvéderm Voluma XC was considered clinically effective if at least 70% of treated subjects were responders, and if the responder rate for subjects treated with Juvéderm Voluma XC was statistically superior to the responder rate for the control group at 6 months.

Table 2 Mid-Face Volume Deficit Scale (MFVDS)

Score	Grade	Description
5	Severe	• Wasting • Severe concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Severe tear troughs and/or nasolabial folds • Significant nasojugal folds and/or prejowl sulcus • Significant prominence of bony landmarks • Significant visibility of underlying musculature
4	Significant	• Significant concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Significant tear troughs and/or nasolabial folds • Moderate nasojugal folds and/or prejowl sulcus • Moderate prominence of bony landmarks • Moderate visibility of musculature
3	Moderate	• Moderate concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Moderate tear troughs and/or nasolabial folds • Mild nasojugal folds and/or prejowl sulcus • Mild prominence of bony landmarks • Mild visibility of musculature
2	Mild	• Mild concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Mild tear troughs and/or nasolabial folds
1	Minimal	• Flattening in the zygomaticomalar region, anteromedial cheek, and/or submalar region
0	None	• Moon face • Fullness (convexity) in the zygomaticomalar region, anteromedial cheek, and/or submalar region

Safety: The presence, location (zygomaticomalar region, anteromedial cheek, and/or submalar region), severity, and duration of common treatment site responses (CTRs) and all adverse events (AEs) were solicited by a 30-day subject diary, by AE case report forms, by telephone/email follow-up at 3 days, by office visits at 30 days after each treatment, and at the scheduled follow-up visits throughout the study. At the time of initial treatment, all subjects also received a subdermal depot injection in the arm or behind the ear for potential biopsy for histological evaluation.

Followup: Post-treatment follow-up occurred at Day 3 as a telephone/email contact, 30-day safety diary, and office visits at 1, 3, and 6 months and at quarterly intervals up to 24 months after the last treatment. The control subjects attended a similar effectiveness schedule at 1, 3, and 6 months. The month 6 visit marked the end of the primary, blinded follow-up period. After the 6-month visit, the control subjects were offered treatment and then followed the same treatment and follow-up schedule as the treatment group subjects. This extended follow-up period for both treatment and control group subjects started at month 6 and continued until 24 months after last treatment (initial or touch-up) or until a subject's overall and individual treatment area MFVDS scores returned to baseline or worse at 12 months or more after last treatment. At the end of the extended follow-up period, an optional repeat treatment was offered to subjects, with an accompanying day 3 telephone/email contact, 30-day safety diary, and assessments at 1, 3, 6, 9, and 12 months after repeat treatment.

Inclusion/Exclusion Criteria

Inclusion

- Male or female, 35-65 years of age
- Signed the IRB-approved Informed Consent form and the HIPAA form prior to any study-related procedures performed
- Had zygomaticomalar region, anteromedial cheek, submalar region, and/or overall mid-facial volume deficit assessed by the TI as grade 3, 4, or 5 on the photometric Mid-Face Volume Deficit Scale (MFVDS)
- Desired cheek augmentation to correct age-related volume deficit in the mid-face, i.e., zygomaticomalar region, anteromedial cheek, and/or submalar region, as recommended by the TI
- Accepted the obligation not to receive any other facial procedures or treatments affecting facial volume deficit at any time during the study
- Was able to follow study instructions and likely to complete all required visits, as assessed by the TI
- If the subject was a female of childbearing potential (sexually active and not sterile nor postmenopausal for at least 1 year), had a urine pregnancy test evaluated as negative within 10 days prior to enrollment, had used contraception for at least 30 days prior to enrollment, and agreed to use a reliable method of contraception for the duration of the study

Exclusion

- Had received (or was planning to receive) anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin), anti-inflammatory drugs (oral/injectable corticosteroids or non-steroid anti-inflammatory drugs, e.g., aspirin, ibuprofen), or other substances known to increase coagulation time (vitamins or herbal supplements, e.g., Vitamin E, garlic, gingko), from 10 days pre- to 3 days post-injection [Study device injections were delayed as necessary to accommodate this 10-day wash-out period.]
- Had undergone cosmetic facial plastic surgery (with the exception of rhinoplasty more than 2 years prior to enrollment), tissue grafting, or tissue augmentation with silicone, fat, or other permanent, or semi-permanent dermal fillers or was planning to undergo any of these procedures at any time during the study
- Had undergone temporary facial dermal filler injections with HA-based fillers within 12 months, porcine-based collagen fillers within 24 months, or neuromodulator injections, mesotherapy, or resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or other ablative or non-ablative procedures) within 6 months prior to entry in the study or was planning to undergo any of these procedures at any time during the study
- Had begun use of any new over-the-counter or prescription, oral or topical, anti-wrinkle products in the treatment area within 90 days prior to enrollment or was planning to begin use of such products at any time during the study. [NOTE: Use of sunscreens and continued therapy with some topical treatments (e.g., alpha hydroxyl acids, glycolic acids, retinol, or retinoic acids) was allowed if the regimen was established ≥ 90 days prior to enrollment]
- Had very thin skin in the mid-facial region, tendency to accumulate fluid in the lower eyelids, or large infraorbital fat pads, i.e., significant convexity or projection from the infraorbital fat pads
- Had mid-face volume deficit due to congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (e.g., juvenile dermatomyositis), partial lipodystrophy (e.g., Barraquer-Simons syndrome), inherited disease, or HIV-related disease
- Had a history of anaphylaxis, multiple severe allergies, atopy, or allergy to lidocaine (or any amide-based anesthetic), HA products, or *Streptococcal* protein, or had plans to undergo desensitization therapy during the term of the study
- Had noticeable acne scarring, an active inflammation, infection, cancerous or precancerous lesion, or unhealed wound or had undergone radiation treatment in the area to be treated

- Was pregnant, lactating, or planning to become pregnant at any time during the study
- Had received any investigational product within 30 days prior to study enrollment or was planning to participate in another investigation during the course of this study
- Was an employee (or a relative of an employee) of the EIs, TI, Sponsor, or representative of the Sponsor
- Had a condition or was in a situation that, in the TI's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study

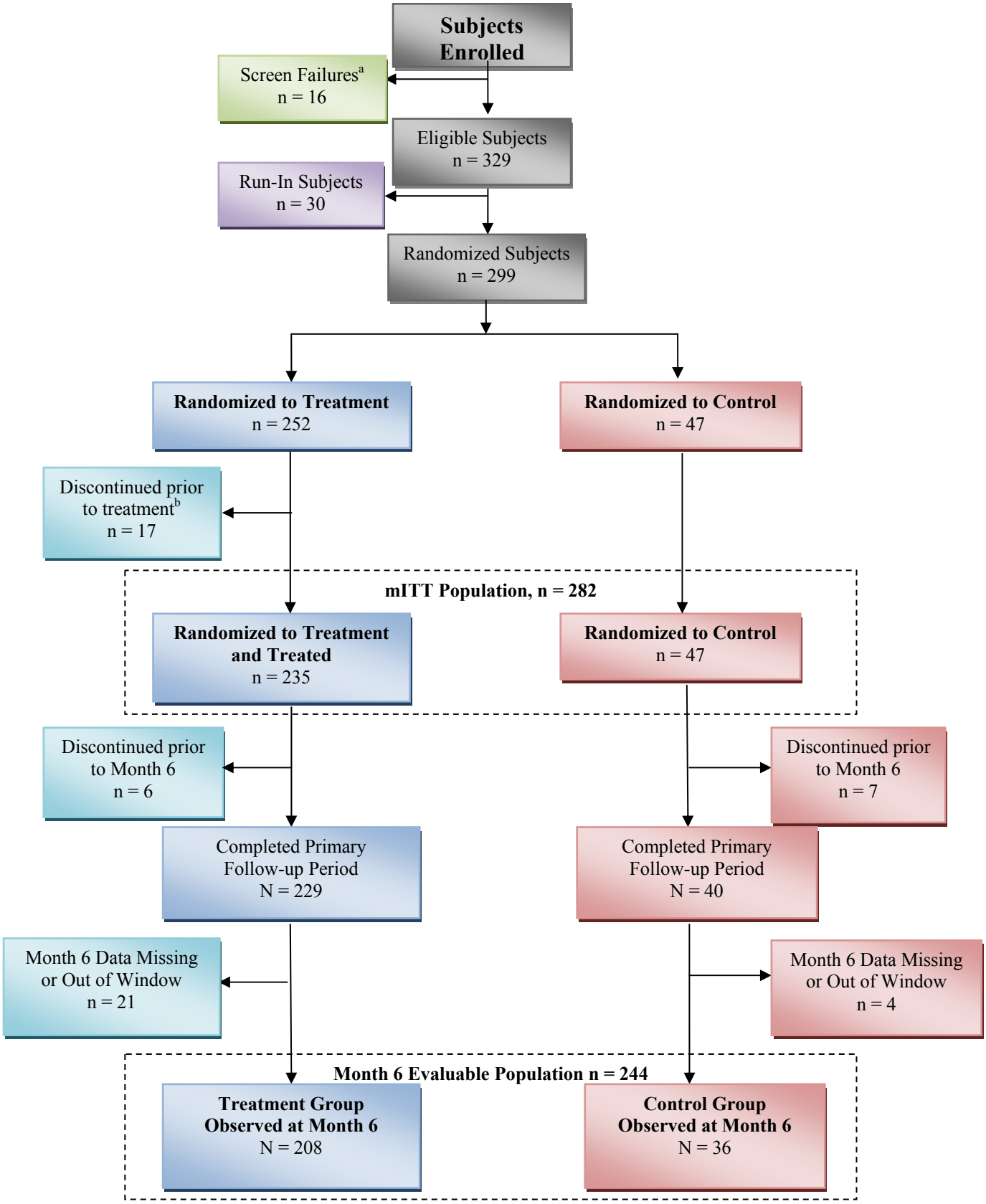
Subject Demographics and Accounting

A total of 345 subjects were enrolled in the study, with 16 subjects who failed screening, 30 subjects assigned as run-in subjects, and 299 subjects randomized per protocol. Of the 299 randomized subjects, 235 were randomized to the treatment group, 47 were randomized to the control group, and 17 subjects were randomized but discontinued prior to treatment, resulting in 282 subjects in the Modified intent-to-treat (mITT) population (Table 3). 6 subjects in the treatment group and 7 subjects in the control group discontinued prior to the end of the Month 6 visit primary, blinded follow-up period. Of the remaining 229 treatment group and 40 control group subjects, 21 treatment group subjects and 4 control group subjects had missing data or were out of window, resulting in 208 and 36 evaluable treatment and control group subjects at Month 6, respectively.

Of the 184 treatment group and 3 control group subjects who were offered the repeat treatment, 124 (67.4% 124/184) of treatment subjects and 1 control subject received the optional retreatment; 38 subjects chose not to receive the repeat treatment. An additional 24 subjects received repeat treatment after the sponsor's database lock for a total of 79.7% of subjects opting for repeat treatment.

Subjects in the mITT population were primarily female (80.1% of 282 subjects), with a median age at study entry of 55 years (range 35 to 65). Slightly more than half were of Caucasian descent (58.5%), and all Fitzpatrick skin types were represented in the study (Table 4).

Table 3 Subject Accounting



[a] Primary reason for screen failure was ineligibility (13 of 16 subjects)
[b] Primary reason for discontinuation prior to treatment was withdrawn consent (11 of 17 subjects)

Table 4 Subject Demographics

Characteristic		ITT (N = 282) % (n/N)	Treatment Group (N = 235) % (n/N)	Control Group (N = 47) % (n/N)
Gender				
	Female	80.1% (226/282)	80.4% (189/235)	78.7% (37/47)
	Male	19.9% (56/282)	19.6% (46/235)	21.3% (10/47)
Age (years)				
	Mean	54.4	54.4	54.7
	Standard Deviation	6.98	7.18	5.95
	Median	55.0	56.0	55.0
	Range (Min, Max)	(35, 65)	(35, 65)	(35, 65)
Race				
	Caucasian	58.5% (165/282)	58.3% (137/235)	59.6% (28/47)
	Hispanic	13.8% (39/282)	14.9% (35/235)	8.5% (4/47)
	African-American	19.9% (56/282)	18.7% (44/235)	25.5% (12/47)
	Asian	4.3% (12/282)	3.8% (9/235)	6.4% (3/47)
	Other[a]	3.5% (10/282)	4.3% (10/235)	0.0% (0/47)
Fitzpatrick Skin Type				
	I	2.8% (8/282)	2.6% (6/235)	4.3% (2/47)
	II	25.5% (72/282)	26.4% (62/235)	21.3% (10/47)
	III	27.7% (78/282)	28.5% (67/235)	23.4% (11/47)
	IV	20.2% (57/282)	18.3% (43/235)	29.8% (14/47)
	V	18.8% (53/282)	18.7% (44/235)	19.1% (9/47)
	VI	5.0% (14/282)	5.5% (13/235)	2.1% (1/47)

Primary Effectiveness Endpoint Results and Statistical Analysis

The primary effectiveness measure was the average of the 2 live and blinded Evaluating Investigators (EI) assessments of the subject's overall mid-face volume deficit using the validated 6-point photometric Mid-Face Volume Deficit Scale (MFVDS). Subjects who demonstrated an average improvement (reduction) of ≥ 1 grade on the MFVDS compared with the average of the pre-treatment assessments were considered "responders." Two primary hypotheses were tested on the responder rate. First, a 2-sided exact binomial test was used to determine if at least 70% of the subjects treated with Juvéderm Voluma XC were responders at 6 months. Second, a 2-group, 2-sided Fisher's exact test was used to determine if the responder rate for the treatment group was statistically superior to the responder rate for the control group at 6 months. Both primary effectiveness endpoints were met (Tables 5 and Figure 2). Significantly greater than 70% of the treatment group were responders (observed responder rate = 86%, $p < 0.0001$), and the responder rate for the treatment group was significantly greater ($p < 0.0001$) than the responder rate for the control group (a difference of 46.7%) at month 6.

The treatment group's median MFVDS improved from 3.5 to 1.5 at 6 months, whereas the control group's median score remained the same (3.0). The mean change from baseline in MFVDS scores was -1.7 (range, -1.80 to -1.57) for the treatment group and -0.6 (range, -0.82 to -0.29) for the control group.

FDA comment: The sponsor validated the Mid-Face Volume Deficit Scale (MFVDS); however, the MFVDS has not been used before for the approval of a medical device. The two live evaluating reviewers often did not agree on the rating of a given subject, as there was exact agreement in less than half of the evaluations (41%). In 15% of 1139 total evaluations, the two evaluators gave assessments that differed by two points or more, including two instances where the two evaluators gave ratings that differed by 4 points. In addition, subjects reported a ≥ 1-point improvement at 6-months in the MFVDS evaluation less frequently than the Independent Evaluators (58% versus 85.6%). The weighted kappa measuring agreement between the two reviewers was 0.65. Please note that all of the agreement measures presented here are based on the blinded evaluations for the overall MFVDS. The MFVDS scores for specific regions and overall MFVDS scores at post-6 month time points showed lower levels of agreement. Table 6 below shows how scores between the two evaluators compared.

Table 5 Primary Effectiveness Analysis (mITT Population)

	Responder Rate at Month 6[a]	97.5% CI	p-value
Treatment Group	85.6% (178/208)	(79.24%, 90.59%)	<0.0001[b]
Control Group[c]	38.9% (14/36)	(21.33%, 58.82%)	
Difference in Responder Rates (Treatment rate - Control rate)	46.7%		<0.0001[d]

[a] Five subjects attended the Month 6 visit but did not have the MFVDS assessment completed and are not included in this table

[b] p-value corresponding to the exact binomial test to demonstrate that responder rate for the treatment group is greater than 70%, where responder rate is the percent of subjects with at least 1-point improvement since baseline based on the average of the 2 EIs' assessments of the subject's overall mid-face volume deficit

[c] Includes 2 subjects who were treated in error

[d] p-value corresponding to the 2-sided 2-group Fisher's exact test to demonstrate that responder rate for the treatment group is superior to that of the control group

The panel will be asked to comment on the reliability of the MFVDS and the meaningfulness of a one point change on this scale. To evaluate the sensitivity of the results to the pre-specified definition of a responder as a one point change, an analysis was done where a responder was defined as a two point change. In the two point responder analysis, 51% of subjects in the treatment group were responders as compared to 11% of subjects in the control group.

Figure 2 Mean Overall MFVDS Score as assessed by EIs.

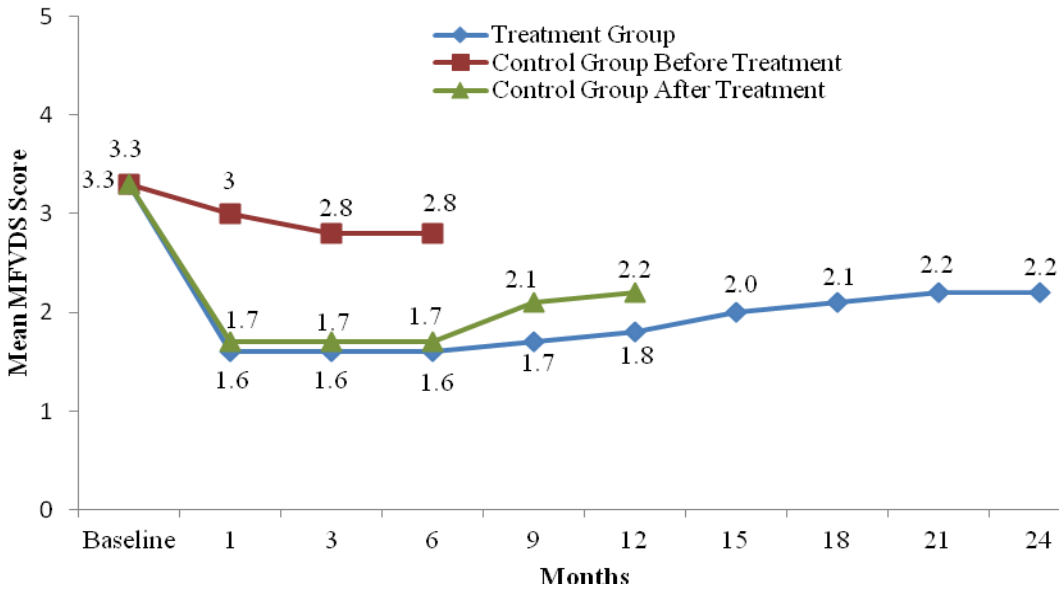


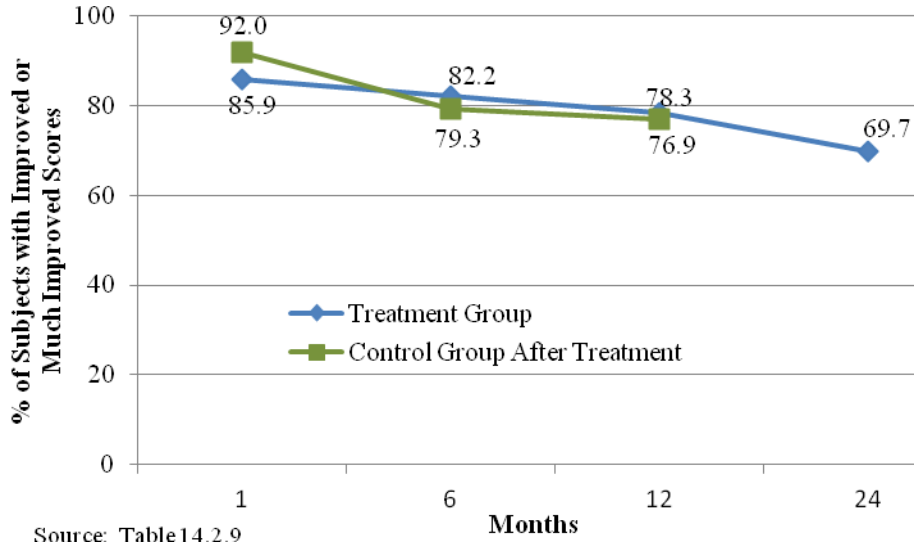
Table 6: Comparison of Evaluators' assessments of MFVDS

	Highest Rating					
Lowest Rating	**0**	**1**	**2**	**3**	**4**	**5**
0	7	61	33	6	0	0
1	0	141	219	83	7	2
2	0	0	88	108	28	1
3	0	0	0	141	97	5
4	0	0	0	0	79	23
5	0	0	0	0	0	10

Key Secondary Effectiveness Endpoints Results

Global Aesthetic Improvement Scale (GAIS): At the 6 month follow-up visit, the EIs independently assessed the subject's level of improvement on the 5-point Global Aesthetic Improvement Scale (GAIS) (Figure 3), comparing the live subject with the subject's pre-treatment digital image. The GAIS responder rate for the treatment group as assessed by EIs at 6 months was 82.2% (171/208), where the responder rate was the percent of subjects with a score of ≥ 1 on the GAIS for overall mid-face volume. According to EI assessments on the GAIS at Month 24, subjects in the treatment group were primarily improved or much improved (69.7% had a score of 1, 1.5, or 2, 108/155).

Figure 3 GAIS Responder Rates



Source: Table14.2.9

Imaging: Comparison of 3D digital imaging results showed that on average there was a 6 to 8 cc increase in the overall mid-face volume for the treatment group (Table 7). Prior to treatment, the control group's mean change was less than 1 cc. After treatment, the 12-month values are comparable to the treatment group (6.8 cc for the treatment group and 7.2 cc for the control group after receiving treatment).

FDA comment: The imaging results appear to show that the volume increased by more than the total volume injected. The control group also increased in volume according to the imaging assessment, though to a much smaller degree.

Table 7 Imaging Assessment of Subject's Mid-face Volume Analysis Sample mITT (N=235 subjects)

		Change in Mid-Face Volume Since Baseline (cc)				
	N	Mean	Median	Standard Deviation	Range (Min, Max)	95% Confidence Interval
Overall Mid-Face Treatment Group						
Month 1	195	8.434	7.798	4.5826	(-3.16, 23.46)	(7.7872, 9.0817)
Month 6	196	6.758	6.498	4.4318	(-6.58, 25.42)	(6.1336, 7.3822)
Month 12	193	6.802	6.796	4.7327	(-7.29, 19.39)	(6.1302, 7.4740)
Month 18	166	6.789	6.874	4.9418	(-4.13, 27.40)	(6.0319, 7.5465)
Month 24	152	7.315	7.095	4.8801	(-5.45, 22.23)	(6.5334, 8.0976)
Control Group						
			Primary Follow-up Period			
Month 1	29	0.594	0.427	3.0661	(-5.39, 12.60)	(-0.5719, 1.7607)
Month 6	29	0.841	0.342	3.0139	(-5.97, 11.60)	(-0.3054, 1.9874)
			Extended Follow-up Period			
Month 12	25	7.201	7.026	6.3007	(-11.78, 17.44)	(4.6001, 9.8017)

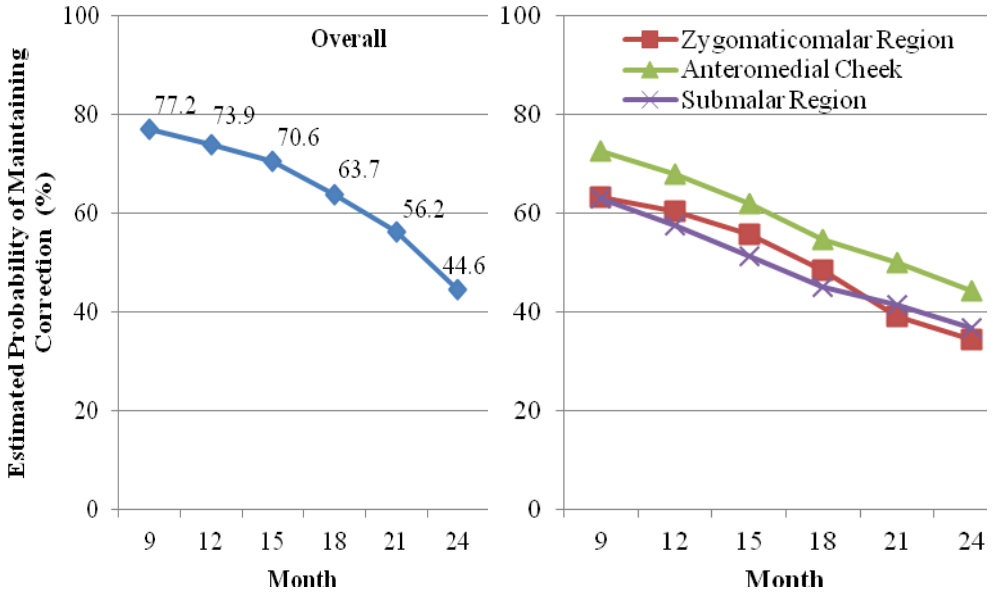
Duration of Effectiveness: 85.6% of subjects received the optional repeat treatment at the month 24-time point (Table 8). Duration of effect was determined using a Kaplan-Meier survival analysis to estimate the probability of retaining at least a 1-point improvement in the volume deficit score. More than half of treated subjects (56.2%) were estimated to maintain duration of effect through Month 21 for the overall treatment, decreasing to 44.6% at Month 24 (Figure 4). When examined by individual treatment area, the anteromedial cheek had slightly higher estimated probabilities of maintaining correction than the zygomaticomalar region and submalar region.

FDA comment: The Juvéderm Voluma XC clinical study does not include a blinded comparison to control after 6-months. The panel will be asked to comment on the ability of the effectiveness measures to detect clinically meaningful product performance in the followup period after the 6-month primary effectiveness time point.

Table 8 Time points when Subjects received repeat treatment

Visit	% (n/N)
Month 12	3.2% (4/125)
Month 15	4.0% (5/125)
Month 18	3.2% (4/125)
Month 21	4.0% (5/125)
Month 24	85.6% (107/125)

Figure 4 Duration of Effectiveness



Subgroup Analysis: The MFVDS and GAIS responder rates were summarized independently for treatment group subgroups defined by gender, race, Fitzpatrick skin type, baseline volume deficit, plane of injection, injection technique, injection volume, geographical region, and investigational site. Table 9 summarizes the subgroups overall MFVDS responder rates at Months 6, 12, and 24 and the GAIS responder rates at Month 6.

FDA comment: There were large differences in the effectiveness between sites (See Figure 5). As the evaluations were live at each site, it is impossible to tell if the site-to site differences are due to treatment differences or evaluator differences. The panel will be asked to comment on the reliability of the MFVDS scale.

Table 9 Subgroup Effectiveness Analysis

Subgroup (N[a])	GAIS Responder Rate at Month 6 %	Overall MFVDS Responder Rate		
		Month 6 %	Month 12 %	Month 24 %
Gender				
Female (169)	79.9	84.0	84.8	66.4
Male (39)	92.3	92.3	87.2	69.7
Race				
Caucasian (124)	91.1	91.9	88.1	70.7
Hispanic (29)	72.4	93.1	90.3	64.0
African-American (38)	65.8	63.2	77.1	53.6
Asian (7)	71.4	100	88.9	100
Other (10)	70.0	60.0	60.0	55.6
Fitzpatrick Skin Type				
I (6)	100	100	100	60.0
II (58)	94.8	93.1	85.5	73.8
III (57)	82.5	89.5	93.2	70.8
IV (36)	80.6	88.9	88.9	70.6
V (41)	65.9	63.4	65.8	48.4

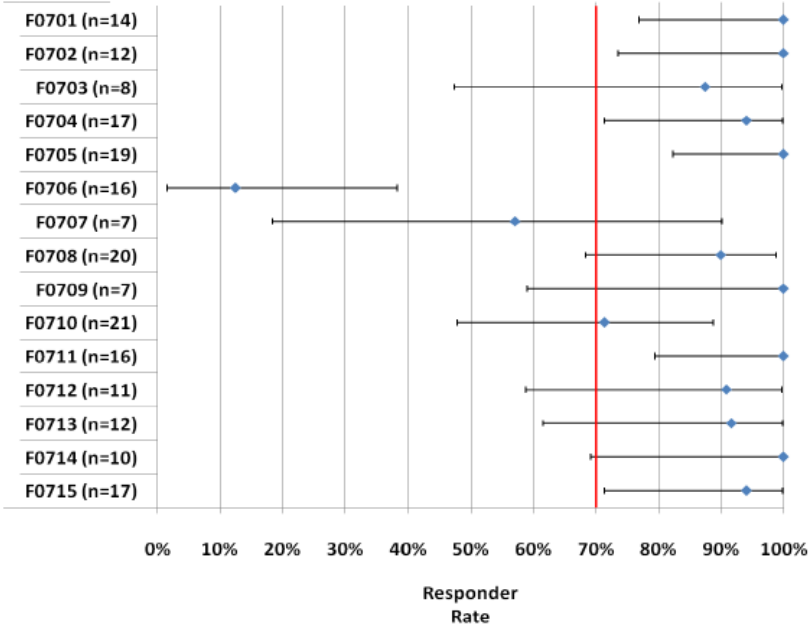
Subgroup (N[a])	GAIS Responder Rate at Month 6 %	Overall MFVDS Responder Rate		
		Month 6 %	Month 12 %	Month 24 %
VI (10)	70.0	90.0	90.0	71.4
Baseline Volume Deficit				
Moderate (103)	75.7	76.7	80.8	61.7
Significant (90)	88.9	96.7	90.9	73.7
Severe (8)	100	100	100	83.3
Plane of Injection				
Subcutaneous (205)	82.9	86.8	85.2	67.5
Supraperiosteal (191)	82.2	84.8	85.3	66.3
Injection Technique				
Retrograde (164)	82.9	82.9	83.1	66.9
Antegrade (113)	88.5	94.7	92.1	75.5
Tunneling (169)	85.2	87.0	85.3	69.5
Fanning (162)	85.8	86.4	85.4	70.5
Other (195)	81.5	85.1	84.7	68.4
Injection Volume				
≤ 6.5 mL (100)	73.0	74.0	77.0	57.0
> 6.5 mL (108)	90.7	96.3	93.2	76.1
Geographical Region				
Northeast (40)	65.0	62.5	69.4	65.4
Southeast (59)	88.1	84.7	78.9	62.7
Midwest (23)	82.6	87.0	100	50.0
Northwest (27)	88.9	96.3	89.3	78.9
Southwest (37)	78.4	97.3	94.7	75.0
Canada (22)	95.5	95.5	91.7	69.6
Investigational Site				
F0701 (14)	100	100	92.3	58.3
F0702 (12)	100	100	100	90.9
F0703 (8)	75.0	87.5	80.0	83.3
F0704 (17)	82.4	94.1	88.2	100
F0705 (19)	94.7	100	94.4	76.9
F0706 (16)	31.3	12.5	25.0	10.0
F0707 (7)	57.1	57.1	100	33.3
F0708 (21)	95.2	90.5	81.8	71.4
F0709 (7)	100	100	100	NR[b]
F0710 (21)	81.0	71.4	68.4	25.0
F0711 (16)	93.8	100	100	53.8
F0712 (11)	27.3	90.9	92.9	77.8
F0713 (12)	91.7	91.7	91.7	45.5
F0714 (10)	100	100	91.7	91.7
F0715 (17)	88.2	94.1	87.5	92.9

NR = No responses

[a] N denotes number of subjects in the subgroup who provided Month 6 assessment

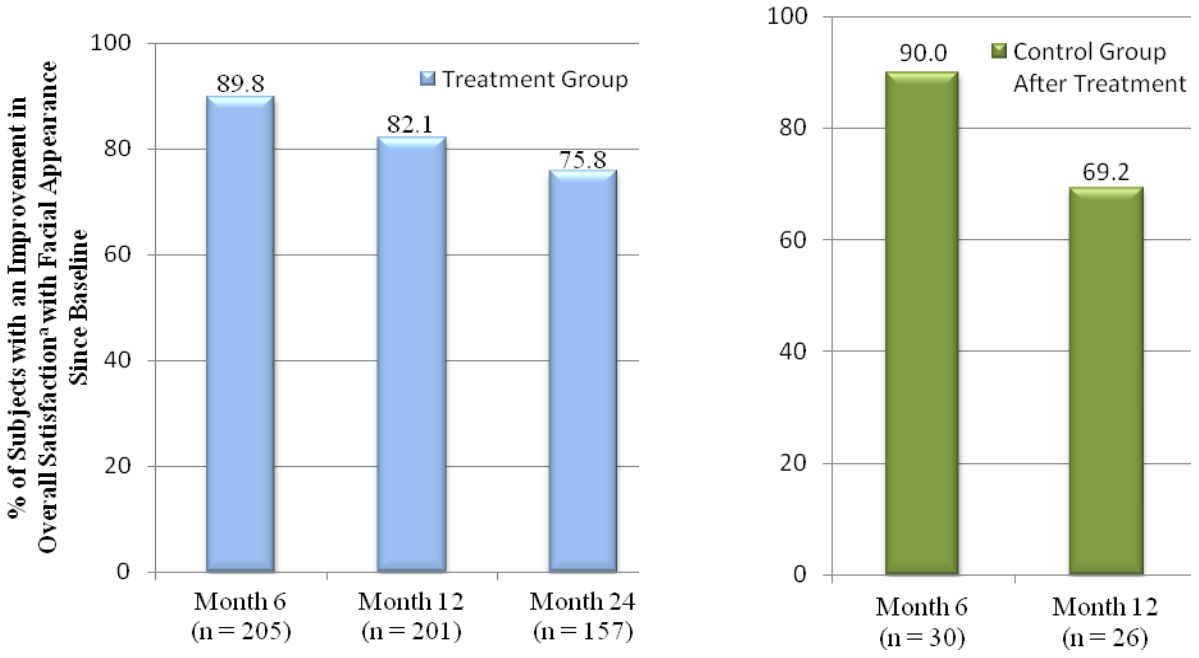
[b] One of the EIs was no longer with the site for the Month 24 evaluations. Since 2 EIs are required for the assessments, there are no data for this site at this timepoint.

Figure 5: Responder Rates by Investigational Sites



Patient Reported Outcomes (PRO): Subjects rated overall satisfaction with their facial appearance. Scores were calculated as the average score (4 points maximum on a 0 to 4 scale) from the responses to the first 6 questions on the Facial Appearance Evaluation (FAE) then multiplied by 25, resulting in a scale from 0 to 100, where 0 represents the least satisfaction and 100 is the greatest satisfaction. At baseline, the mean score was 38.5 for the treatment group and 38.1 for the control group. Mean scores for the treatment group increased to 61.9, 58.5, and 53.5 at Months 6, 12, and 24, respectively. More than three-fourths of the treatment group subjects at each time point demonstrated an improvement in the overall satisfaction score since baseline, and more than two-thirds of the control group subjects demonstrated improvement after treatment (Figure 6).

Figure 6 Subjects' Overall Satisfaction with Facial Appearance



[a] Overall score is obtained as average score for responses on first 6 questions on FAE form multiplied by 25. It ranges from 0 to 100, where 0 represents the least and 100 represents the most satisfaction. Improvement indicates an increase in the overall satisfaction score since baseline.

MFVDS Subject Assessment: 58% (120/207) of subjects reported a ≥ 1-point improvement at 6-months in the MFVDS compared to 85.6% (178/208) with a ≥ 1-point improvement at 6-months reported by the EIs.

Repeat treatment: As of the sponsor's PMA submission, 67.4% (124/184) of treatment group subjects and 1 of 3 eligible control subjects have accepted the optional retreatment. 38 subjects declined the optional repeat treatment with a majority of these subjects not providing a reason for declining the optional repeat treatment. An additional 24 subjects received repeat treatment after the sponsor's database lock for a total of 79.7% of subjects opting for repeat treatment.

Missing Data: Figure 7 shows the various scenarios with data imputation. In all cases except for "all missing as failure" and "worst case," the responder rates for the treatment group are above the a priori 70% lower limit.

FDA comment: The data appear to be robust to missing data assumptions.

Figure 7: Data Imputation Scenarios for the Month 6 Responder Rate

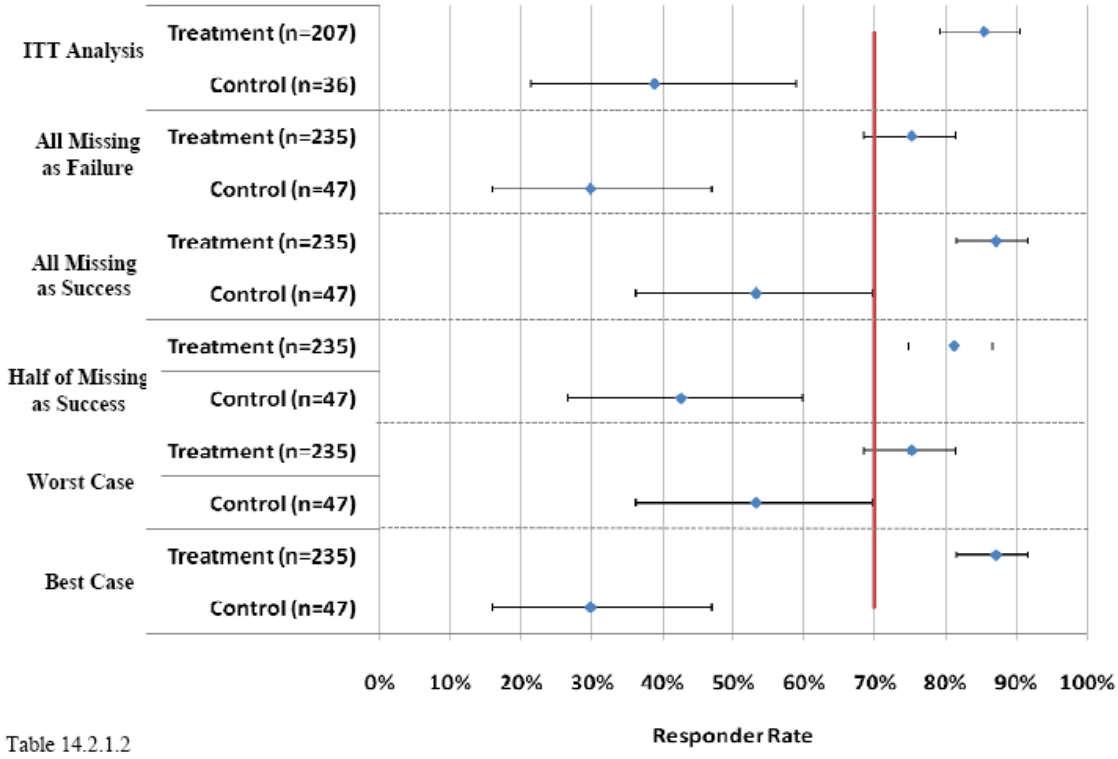


Table 14.2.1.2

FDA Comments on Effectiveness

- Juvéderm Voluma XC met the pre-specified primary endpoint, and the secondary endpoints support product effectiveness. FDA concludes the balance of the evidence indicates that Juvéderm Voluma XC is effective in correcting volume deficit in the mid-face at the 6-month primary effectiveness time point.

- The use of a concurrent no-treatment control group used in this study is considered appropriate because at the time of Investigational Device Exemption (IDE) submission to FDA, there were no products approved by the FDA for these indications to serve as a control.

- 58.5% of subjects in this study were of Caucasian descent. Fitzpatrick skin type enrollment targets were met including 57/235 skin types V and VI.

- There were 61 subjects in the treatment group who discontinued the study: 1/61 ineligibility, 21/61 lost to followup, 2/61 adverse event, 22/61 consent withdrawn, 2/61 discontinued by investigator, 13/61 early discontinuation without loss of mid-face volume.

- The MFVDS scale was validated by the sponsor. However, in the Juvéderm Voluma XC clinical study, evaluators often did not agree on the rating of a single subject, and there were large differences in effectiveness between sites.

Safety Outcomes

The presence, location (zygomaticomalar region, anteromedial cheek, and/or submalar region), severity, and duration of common treatment site responses (CTRs) and adverse events (AEs) were collected with a 30-day subject diary, AE case report forms, telephone/email follow-up at 3 days, by office visits at 30 days after each treatment, and the scheduled follow-up visits throughout the study. CTRs were tabulated by maximum severity, maximum duration, and location separately for initial and touch-up treatments. Adverse events (AEs) were defined as CTRs ongoing at the end of the 30-day diary or reported by the TI at any time during the course of the study, and were tabulated by location and duration as well as the Investigator's assessment of severity, causality, action taken, relationship to study injection/device, and outcome.

Common Treatment Site Responses (CTRs): Of the 265 subjects who completed safety diaries after the initial treatment, 260 (98.1%) reported at least one common treatment site response (CTR). The most frequently reported CTRs at initial treatment were tenderness (92.1% of subjects), swelling (85.7% of subjects), and firmness (82.3% of subjects) (Table 10). 78.4% of CTRs had a maximum severity of moderate (59.2%) to severe (19.2%). CTRs lasted greater than 30 days in 20% of subjects, with lumps/bumps reported most frequently (Table 11). Compared to the initial treatment (98.1%), the frequency of CTRs was generally lower after touch-up and repeat treatment (91.5% and 90.7% of subjects, respectively).

Definitions for the classification of severity (either as CTR or AE) are shown below:

- Mild: symptoms are barely noticeable or do not make the subject uncomfortable. The AE/CTR does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
- Moderate: symptoms are of sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) with prescription drugs or therapies may be needed.
- Severe: Symptoms are of sufficient severity to cause the subject severe discomfort. Performance of daily activities is compromised. Treatment for symptom(s) with prescription drugs or therapies may be needed.

Table 10 Self-Reported CTRs by Maximum Severity

		Severity[a]		
CTR[b]	% (n/N)	Mild % (n/N)	Moderate % (n/N)	Severe % (n/N)
Initial Treatment (N = 265)[c]				
Any CTR	98.1% (260/265)	21.5% (56/260)	59.2% (154/260)	19.2% (50/260)
Tenderness	92.1% (244/265)	46.3% (113/244)	50.0% (122/244)	3.7% (9/244)
Swelling	85.7% (227/265)	46.7% (106/227)	43.6% (99/227)	9.7% (22/227)
Firmness	82.3% (218/265)	37.6% (82/218)	54.6% (119/218)	7.8% (17/218)
Lumps/Bumps	81.1% (215/265)	41.4% (89/215)	48.8% (105/215)	9.8% (21/215)
Bruising	77.7% (206/265)	37.4% (77/206)	51.5% (106/206)	11.2% (23/206)
Pain	66.4% (176/265)	59.1% (104/176)	38.6% (68/176)	2.3% (4/176)
Redness	66.0% (175/265)	60.0% (105/175)	36.0% (63/175)	4.0% (7/175)
Discoloration	41.1% (109/265)	62.4% (68/109)	27.5% (30/109)	10.1% (11/109)
Itching	38.5% (102/265)	70.6% (72/102)	18.6% (19/102)	10.8% (11/102)
Other	12.5% (33/265)	51.5% (17/33)	30.3% (10/33)	18.2% (6/33)
Touch-up Treatment (N = 212)[c]				
Any CTR	91.5% (194/212)	48.5% (94/194)	41.2% (80/194)	10.3% (20/194)
Tenderness	73.6% (156/212)	62.2% (97/156)	32.1% (50/156)	5.8% (9/156)
Swelling	64.2% (136/212)	58.8% (80/136)	36.8% (50/136)	4.4% (6/136)
Lumps/Bumps	54.7% (116/212)	65.5% (76/116)	30.2% (35/116)	4.3% (5/116)
Bruising	54.2% (115/212)	60.0% (69/115)	33.0% (38/115)	7.0% (8/115)
Firmness	52.8% (112/212)	60.7% (68/112)	34.8% (39/112)	4.5% (5/112)
Pain	45.3% (96/212)	70.8% (68/96)	25.0% (24/96)	4.2% (4/96)
Redness	45.3% (96/212)	76.0% (73/96)	21.9% (21/96)	2.1% (2/96)
Discoloration	21.7% (46/212)	69.6% (32/46)	17.4% (8/46)	13.0% (6/46)
Itching	21.2% (45/212)	80.0% (36/45)	13.3% (6/45)	6.7% (3/45)
Other	4.7% (10/212)	40.0% (4/10)	50.0% (5/10)	10.0% (1/10)
Repeat Treatment (N = 120)[c]				
Any CTR	90.0% (108/120)	35.2% (38/108)	50.0% (54/108)	14.8% (16/108)
Tenderness	75.0% (90/120)	53.3% (48/90)	42.2% (38/90)	4.4% (4/90)
Swelling	65.8% (79/120)	49.4 (39/79)	48.1% (38/79)	2.5% (2/79)
Firmness	68.3% (82/120)	46.3% (38/82)	51.2% (42/82)	2.4% (2/82)
Lumps/Bumps	60.0% (72/120)	51.4% (37/72)	43.1% (31/72)	5.6% (4/72)
Bruising	60.0% (72/120)	52.8% (38/72)	33.3% (24/72)	13.9% (10/72)
Pain	55.8% (67/120)	62.7% (42/67)	32.8% (22/67)	4.5% (3/67)
Redness	54.2% (65/120)	60.0% (39/65)	36.9% (24/65)	3.1% (2/65)
Discoloration	23.3% (28/120)	75.0% (21/28)	25.0% (7/28)	0.0% (0/28)
Itching	32.5% (39/120)	79.5% (31/39)	20.5% (8/39)	0.0% (0/36)
Other	7.5% (9/120)	77.8% (7/9)	22.0% (2/9)	0.0% (0/9)

[a] Maximum reported severity in the diary. The denominator for percentages by severity is the number of subjects with the corresponding CTR.

[b] CTRs are listed in decreasing order of frequency of occurrence

[c] N denotes number of subjects who recorded entries in their diaries after treatment

Table 11 Self-Reported CTRs by Maximum Duration

		Duration[a]				
		1-3 Days	4-7 Days	8-14 Days	15-30 Days	>30 Days
CTR[b]	% (n/N)	% (n)	% (n)	% (n)	% (n)	% (n)
Initial Treatment (N = 265)[c]						
Any CTR	98.1% (260/265)	8.1% (21)	22.7% (59)	24.6% (64)	24.6% (64)	20.0% (52)
Tenderness	92.1% (244/265)	29.9% (73)	30.7% (75)	27.9% (68)	8.6% (21)	2.9% (7)
Swelling	85.7% (227/265)	41.0% (93)	33.0% (75)	17.6% (40)	5.3% (12)	3.1% (7)

Firmness	82.3% (218/265)	26.6% (58)	29.8% (65)	20.2% (44)	11.0% (24)	12.4% (27)
Lumps/Bumps	81.1% (215/265)	21.4% (46)	22.3% (48)	22.3% (48)	18.1% (39)	15.8% (34)
Bruising	77.7% (206/265)	24.8% (51)	30.6% (63)	29.6% (61)	14.6% (30)	0.5% (1)
Pain	66.4% (176/265)	56.3% (99)	31.3% (55)	9.7% (17)	2.8% (5)	0
Redness	66.0% (175/265)	59.4% (104)	28.0% (49)	8.6% (15)	2.3% (4)	1.7% (3)
Discoloration	41.1% (109/265)	64.2% (70)	19.3% (21)	6.4% (7)	5.5% (6)	4.6% (5)
Itching	38.5% (102/265)	81.4% (83)	16.7% (17)	2.0% (2)	0	0
Other	12.5% (33/265)	66.7% (22)	15.2% (5)	3.0% (1)	12.1% (4)	3.0% (1)
Touch-up Treatment (N = 212)[c]						
Any CTR	91.5% (194/212)	20.6% (40)	32.5% (63)	27.3% (53)	12.9% (25)	6.7% (13)
Tenderness	73.6% (156/212)	39.1% (61)	34.0% (53)	21.2% (33)	4.5% (7)	1.3% (2)
Swelling	64.2% (136/212)	41.2% (56)	42.6% (58)	12.5% (17)	1.5% (2)	2.2% (3)
Lumps/Bumps	54.7% (116/212)	37.1% (43)	28.4% (33)	16.4% (19)	12.1% (14)	6.0% (7)
Bruising	54.2% (115/212)	28.7% (33)	39.1% (45)	25.2% (29)	6.1% (7)	0.9% (1)
Firmness	52.8% (112/212)	37.5% (42)	33.9% (38)	16.1% (18)	9.8% (11)	2.7% (3)
Redness	45.3% (96/212)	62.5% (60)	27.1% (26)	8.3% (8)	2.1% (2)	0
Pain	45.3% (96/212)	62.5% (60)	24.0% (23)	12.5% (12)	0	1.0% (1)
Discoloration	21.7% (46/212)	69.6% (32)	15.2% (7)	13.0% (6)	0	2.2% (1)
Itching	21.2% (45/212)	88.9% (40)	4.4% (2)	4.4% (2)	0	2.2% (1)
Other	4.7% (10/212)	50.0% (5)	20.0% (2)	10.0% (1)	10.0% (1)	10.0% (1)
Repeat Treatment (N = 120)[c]						
Any CTR	90.0% (108/120)	20.4% (22/108)	32.4% (35/108)	21.3% (23/108)	20.4% (22/108)	5.6% (6/108)
Tenderness	75.0% (90/120)	40.0% (36/90)	35.6% (32/90)	11.1% (10/90)	12.2% (11/90)	1.1% (1/90)
Swelling	65.8% (79/120)	64.6% (51/79)	21.5% (17/79)	7.6% (6/79)	5.1% (4/79)	1.3% (1/79)
Firmness	68.3% (82/120)	28.0% (23/82)	36.6% (30/82)	18.3% (15/82)	12.2% (10/82)	4.9% (4/82)
Lumps/Bumps	60.0% (72/120)	41.7% (30/72)	29.2% (21/72)	11.1% (8/72)	12.5% (9/72)	5.6% (4/72)
Bruising	60.0% (72/120)	38.9% (28/72)	34.7% (25/72)	18.1% (13/72)	8.3% (6/72)	0.0% (0/72)
Pain	55.8% (67/120)	64.2% (43/67)	23.9% (16/67)	10.4% (7/67)	1.5% (1/67)	0.0% (0/67)
Redness	54.2% (65/120)	56.9% (37/65)	30.8% (20/65)	9.2% (6/65)	3.1% (2/65)	0.0% (0/65)
Discoloration	23.3% (28/120)	85.7% (24/28)	3.6% (1/28)	3.6% (1/28)	7.1% (2/28)	0.0% (0/28)
Itching	32.5% (39/120)	82.1% (32/39)	15.4% (6/39)	2.6% (1/39)	0.0% (0/39)	0.0% (0/39)
Other	7.5% (9/120)	77.8% (7/9)	11.1% (1/9)	0.0% (0/9)	11.1% (1/9)	0.0% (0/9)

[a] Maximum reported successive occurrence of a CTR. Denominator for percentages by duration is the number of subjects with corresponding CTR.

[b] CTRs are listed in decreasing order of frequency of occurrence

[c] N denotes number of subjects who recorded entries in their diaries after the treatment

Adverse Events (AEs): AEs consisted of CTRs ongoing at the end of the 30-day diary (pre-defined as AEs). AEs were also reported directly by the investigator. A subject could have multiple AEs with each attributed to a different cause, severity, action taken, duration, or resolution. Among the 270 treated mITT subjects, 51.9% of subjects (140/270) experienced 855 AEs before repeat treatment (Table 12). 96 subjects (35.6%) experienced an AE at an injection site, and 81 subjects (30.0%) experienced an AE at site other than the injection site.

Before repeat treatment, 58/270 mITT subjects (21.5%) experienced 361 AEs determined by the TI to be caused by Juvéderm Voluma XC (Table 13). After the initial and touch-up treatment, 102 subjects had 427 events that were mild, 72 subjects had 328 events that were moderate in severity, and 21 subjects had 98 events that were severe. After the initial and touch-up treatments, no action was required for 36.7% (99/270) of subjects. For those subjects that required action, interventions included medication (68 subjects), non-drug therapy (24 subjects), and other actions (8 subjects). After the initial and touch up treatments, 95.0% (133/140) of subjects had their events resolve without sequelae. As of the cutoff date, 23 subjects had 39 adverse events that are not yet resolved. with 2 of these subjects experiencing device-related AEs (1 subject with swelling and 1 subject with firmness). The AE of swelling was reported to

have resolved after the cut-off date. The AE of firmness has not yet resolved, however the subject reported satisfaction with her outcome.

Adverse Event Duration (Tables 14.3.23.7-10):

- 44/270 subjects (16.3%) had 271 injection site related AEs with durations lasting 31-60 days
- 17/270 subjects (6.3%) had 100 injection site related AEs with durations lasting 61-90 days
- 7/270 subjects (2.6%) had 34 injection site related AEs with durations lasting 91-180 days
- 6/270 subjects (2.2%) had 25 injection site related AEs with durations lasting greater than 180-days.

Table 12 Adverse Events with Onset before Retreatment with Incidence >1%

	Treated mITT Subjects (N = 270)		
System Organ Class/ Preferred Term[a]	**Subjects % (n/N)**	**95% Confidence Interval**	**Events % (n/N[b])**
One or More Adverse Event	51.9% (140/270)	(45.71%, 57.95%)	100.0% (855/855)
General disorders and administration site conditions	35.9% (97/270)	(30.20%, 41.96%)	80.6% (689/855)
Injection site mass	19.6% (53/270)	(15.06%, 24.88%)	20.5% (175/855)
Injection site induration	14.1% (38/270)	(10.16%, 18.80%)	23.2% (198/855)
Injection site swelling	7.4% (20/270)	(4.58%, 11.21%)	9.0% (77/855)
Injection site pain	6.3% (17/270)	(3.71%, 9.89%)	7.8% (67/855)
Injection site discoloration	3.7% (10/270)	(1.79%, 6.71%)	3.9% (33/855)
Injection site hematoma	3.7% (10/270)	(1.79%, 6.71%)	3.9% (33/855)
Injection site erythema	2.6% (7/270)	(1.05%, 5.27%)	2.8% (24/855)
Injection site rash	1.5% (4/270)	(0.41%, 3.75%)	1.6% (14/855)
Injection site reaction	1.5% (4/270)	(0.41%, 3.75%)	2.8% (24/855)
Infections and infestations	9.3% (25/270)	(6.08%, 13.36%)	4.2% (36/855)
Nasopharyngitis	1.9% (5/270)	(0.60%, 4.27%)	0.6% (5/855)
Bronchitis	1.5% (4/270)	(0.41%, 3.75%)	0.5% (4/855)
Sinusitis	1.5% (4/270)	(0.41%, 3.75%)	0.5% (4/855)
Influenza	1.1% (3/270)	(0.23%, 3.21%)	0.4% (3/855)
Upper respiratory tract infection	1.1% (3/270)	(0.23%, 3.21%)	0.6% (5/855)
Urinary tract infection	1.1% (3/270)	(0.23%, 3.21%)	0.4% (3/855)
Skin and subcutaneous tissue disorders	7.0% (19/270)	(4.29%, 10.77%)	3.3% (28/855)
Dermatitis	1.1% (3/270)	(0.23%, 3.21%)	0.4% (3/855)
Skin discolouration	1.1% (3/270)	(0.23%, 3.21%)	0.4% (3/855)
Injury, poisoning and procedural complications	4.8% (13/270)	(2.59%, 8.09%)	2.6% (22/855)
Contusion	1.1% (3/270)	(0.23%, 3.21%)	0.5% (4/855)
Procedural pain	1.1% (3/270)	(0.23%, 3.21%)	0.5% (4/855)
Nervous system disorders	4.4% (12/270)	(2.32%, 7.63%)	1.4% (12/855)
Headache	1.9% (5/270)	(0.60%, 4.27%)	0.6% (5/855)
Respiratory, thoracic and mediastinal disorders	2.2% (6/270)	(0.82%, 4.77%)	0.8% (7/855)
Asthma	1.1% (3/270)	(0.23%, 3.21%)	0.4% (3/855)

[a] AEs are listed in decreasing order of frequency of occurrence, by System Organ Class and Preferred Term. Verbatim terms indicating lumps or bumps were coded to the preferred term of injection site mass.

[b] N denotes total number of post-treatment AEs. If a subject reports the same AE at multiple injection sites, a separate event is counted for each injection site.

Table 13 Adverse Events caused by Juvéderm Voluma XC

	Before Repeat Treatment		After Repeat Treatment	
System Organ Class/ Preferred Term[a]	**Subjects % (n/N)**	**Events % (n/N[b])**	**Subjects % (n/N)**	**Events % (n/N[b])**
One or More Adverse Event	21.5% (58/270)	100.0% (361/361)	4.8% (6/125)	100.0% (45/45)
General disorders and administration site conditions	21.5% (58/270)	100.0% (361/361)	4.8% (6/125)	100.0% (45/45)
Injection site mass	14.4% (39/270)	37.1% (134/361)	2.4% (3/125)	28.9% (13/45)
Injection site induration	9.6% (26/270)	36.8% (133/361)	3.2% (4/125)	44.4% (20/45)
Injection site swelling	3.0% (8/270)	9.4% (34/361)	0.8% (1/125)	13.3% (6/45)
Injection site pain	1.9% (5/270)	5.3% (19/361)	0.8% (1/125)	13.3% (6/45)
Injection site discoloration	1.1% (3/270)	4.2% (15/361)		
Injection site erythema	1.1% (3/270)	2.2% (8/361)		
Injection site hematoma	0.7% (2/270)	1.9% (7/361)		
Injection site nodule	0.7% (2/270)	1.1% (4/361)		
Inflammation	0.4% (1/270)	0.3% (1/361)		
Injection site reaction	0.4% (1/270)	1.7% (6/361)		

[a] AEs by subject are listed in decreasing order of frequency of occurrence, by System Organ Class and Preferred Term
[b] N denotes total number of post-treatment AEs. If a subject reports the same AE at multiple injection sites, a separate event is counted for each injection site

Serious Adverse events (SAEs): 11 mITT subjects experienced 16 SAEs with onset after initial treatment but before repeat treatment. 3 SAEs (2 subjects) were related to the device, and the other serious adverse events were not classified as device related by the TI. The 3 device related SAEs included:

- Lumps at injection sites that were treated with hyaluronidase and resolved with sequelae of a scar from the biopsy site. Onset at 7-months post treatment.
- Inflammatory reaction under the eye that was treated with hyaluronidase and resolved. Onset at 6-months post-treatment.
- Nodularity in the cheek that was treated with hyaluronidase and resolved. Onset at 7-months post-treatment.

FDA comment: One subject experienced ischemic optic neuropathy caused by an optic nerve stroke approximately 8 months after the initial treatment. The subject was a 60-year old female who was treated with 6 cc of Juvéderm Voluma XC on initial treatment with no subsequent touch up. The subject presented with a 4-week history of vision loss in the right eye. The subject was referred to a neuroophthalmologist who documented a right altitudinal field loss and incidental left optic neuropathy. The MRI and MRA were normal and the carotid Doppler was normal with minimal plaque. The subject was presumed to have had a hemi retinal artery occlusion and a previous optic neuropathy. The subject's medications included Prempro, Imitrex, Nexium, and Singulair.

The Treating Investigator assessed the event to not be caused by Juvéderm Voluma XC. FDA is not able to definitively conclude this event was not device related.

Repeat treatment: The safety profile of Juvéderm Voluma XC after the repeat treatment is consistent with the safety profile observed after the initial treatment. Similar CTRs were observed after the repeat treatment compared to those after the initial treatment. The severity of CTRs was similar between initial and repeat treatments; however, the incidence was lower after repeat treatment, and CTRs lasted for a shorter duration (Tables 10 and 11). Of the 125 subjects who recieved repeat treatments, 8 (6.4%) experienced 57 AEs after the repeat treatment. All AEs after repeat treatment resolved without sequelae.

Biopsies: Twenty-one biopsies from subdermal depot injections in either the forearm or behind the ear were evaluated by a board-certified dermatopathologist. At least one biopsy was obtained from each of the nine study follow-up visit time points. The dermis and subcutaneous tissue were evaluated for fibrosis, inflammation, and implant material. The implant material stained blue in the hematoxylin and eosin sections and was positive for colloidal iron. These qualities were utilized to determine the presence or absence of implant material. The implant was absent in two-thirds of the samples (66.7%, 14/21). Lymphocytes and histiocytes were observed in all of the samples. Scant or mild inflammation was present in nearly all samples (95.2%, 20/21), and mild to moderate fibrosis was present in three-fourths of the samples (76.2%, 16/21).

Subgroup Adverse Event Analysis: The subgroup analysis did not identify differences in the incidence of device related AEs for the different planes of injection (subcutaneous or supraperiosteal), or injection techniques (Table 14). A significant increase in the incidence of device related AEs was identified with increased injection volume (Tables 15 and 16).

Table 14: Subgroup Analysis of Device related Adverse Events with onset prior to repeat treatment

Subgroup	Incidence Rate[a]	95% Confidence Interval
Gender		
Female	34.9% (75/215)	(28.53%, 41.66%)
Male	23.6% (13/55)	(13.23%, 37.02%)
Race		
Caucasian	27.5% (44/160)	(20.75%, 35.11%)
Hispanic	45.9% (17/37)	(29.49%, 63.08%)
African-American	35.8% (19/53)	(23.14%, 50.20%)
Asian	50.0% (5/10)	(18.71%, 81.29%)
Other	30.0% (3/10)	(6.67%, 65.25%)
Fitzpatrick Skin Phototype		
I	14.3% (1/7)	(0.36%, 57.87%)
II	30.0% (21/70)	(19.62%, 42.13%)
III	36.8% (28/76)	(26.06%, 48.69%)
IV	31.5% (17/54)	(19.52%, 45.55%)
V	30.6% (15/49)	(18.25%, 45.42%)
VI	42.9% (6/14)	(17.66%, 71.14%)
Baseline Volume Deficit[b]		
Moderate	30.7% (42/137)	(23.07%, 39.10%)
Significant	37.4% (43/115)	(28.55%, 46.90%)
Severe	20.0% (2/10)	(2.52%, 55.61%)

[a] Denominator for percentages is the number of treated subjects in the subgroup
[b] Treating Investigator's assessment of overall mid-face volume deficit at baseline
[c] Subgroup by plane of injection or injection technique includes subjects who got that particular plane of injection or injection technique at any treatment area at initial or touch-up treatment

Subgroup	Incidence Rate[a]	95% Confidence Interval
Plane of Injection[c]		
Subcutaneous	32.3% (86/266)	(26.75%, 38.31%)
Supraperiosteal	31.9% (79/248)	(26.10%, 38.05%)
Injection Technique[c]		
Tunneling	30.0% (65/217)	(23.94%, 36.52%)
Retrograde	29.5% (61/207)	(23.35%, 36.18%)
Antegrade	32.2% (47/146)	(24.71%, 40.42%)
Fanning	32.5% (68/209)	(26.23%, 39.34%)
Serial Puncture	31.9% (67/210)	(25.66%, 38.67%)
Cross-hatching	27.3% (38/139)	(20.13%, 35.54%)
Ferning	23.5% (4/17)	(6.81%, 49.90%)
Volume Injected (mL)		
≤ median	29.6% (40/135)	(22.08%, 38.09%)
> median	35.6% (48/135)	(27.51%, 44.25%)

[a] Denominator for percentages is the number of treated subjects in the subgroup
[b] Treating Investigator's assessment of overall mid-face volume deficit at baseline
[c] Subgroup by plane of injection or injection technique includes subjects who received treatment in that particular plane of injection or injection technique at any treatment area at the initial or touch-up treatment

Injection volume analysis: There is a significant increase in the incidence of device related AEs with increased injection volume (p=0.0117) and increased age (p=0.0173) based on the results of a multiple logistic regression of incidence of device-related AEs on baseline, demographic, and treatment-related covariates (Tables 15 and 16), with a correlation between injection volume and swelling and bruising.

Table 15 Incidence of Device Related AEs by Injection Volume and Age

Total Volume Injected	AE Rate
< 6 mL	28% (32/115)
6 mL - <9 mL	34% (30/88)
≥9 mL	39% (26/67)

Age	AE Rate
<50	23% (14/62)
50 - <60	31% (41/133)
≥60	44% (33/75)

Table 16 Relationship between Injection Volume and CTR Rate

Volume Injected	Incidence rate of Swelling % (n/N)	95% CI	Incidence Rate of Bruising % (n/N)	95% CI
≤4.6 mL	79.4% (54/68)	(67.88%, 88.26%)	72.1% (49/68)	(59.85%, 82.27%)
>4.6 – ≤6.58 mL	89.1% (57/64)	(78.75%, 95.49%)	81.3% (52/64)	(69.54%, 89.92%)
>6.58mL – ≤8.95 mL	92.5% (62/67)	(83.44%, 97.53%)	83.6% (56/67)	(72.52%, 91.51%)
>8.95 mL	94.0% (63/67)	(85.41%, 98.35%)	91.0% (61/67)	(81.52%, 96.64%)
Overall	88.7% (236/266)		82.0% (218/266)	

FDA Comments on Safety

- The most frequent CTRs reported by subjects were tenderness, swelling, and firmness. CTRs lasted 15-30 days in 24.6% of subjects, and 78.4% of CTRs were moderate to severe.

- Common treatment site responses continued in 20.0% of subjects beyond 30 days becoming classified as AEs, with the most frequent responses being injection site mass and induration.

- The incidence of CTRs decreased for subjects receiving touch-up and repeat treatments.

- 52.8% of treatment subjects (124/235) received the optional retreatment at the end of the extended followup period suggesting these subjects perceived an acceptable benefit/risk profile for the continued use of Juvéderm Voluma XC.

- There were no unexpected histological findings in the biopsy samples.

- Common treatment site responses (CTRs) continued in 20.0% of subjects beyond 30 days. FDA will request Panel comment on the duration and severity of treatment site responses to Juvéderm Voluma XC, and the affect this rate of adverse events has on the overall safety profile of Juvéderm Voluma XC.

- The physician instructions section of the Juvéderm Voluma XC labeling states that common treatment site responses and adverse events may be more likely when injecting high volumes (9mL or greater) and in older patients. FDA will request Panel comment on the safety of Juvéderm Voluma XC over the injection volume range used in the clinical study (1-13.9 mL, mean 6.6 mL), and the adequacy of the label.

V-Supplemental Clinical Experience

Australian Clinical Study:[1] The sponsor has conducted an open label study (VOL-AP01) in Australia to evaluate the safety and effectiveness of Juvéderm Voluma (without lidocaine) in subjects with moderate to significant mid-face volume deficit. This formulation is identical to Voluma (with Lidocaine) with regard to all product specifications, other than the 0.3% lidocaine.

101 subjects were treated with Voluma to treat age-related mid-face volume deficit. Juvéderm Voluma was delivered using either a cannula (53%) or a needle (47%). Subjects attended follow-up visits at weeks 4 (with optional touch-up), 8, 24, 78, and 104 from the initial treatment, with an optional retreatment at the Week 78 or 104 visits. The primary effectiveness measure was the improvement in facial fullness, using an unmasked MFVDS. Additional effectiveness measures included subject and Investigator assessments on the GAIS. The incidence and severity of AEs related to Juvéderm Voluma and its administration, as reported by the subject and as documented by the Investigator, were collected (Table 17). After treatment with Voluma, the most common AEs were bruising, swelling, pain/tenderness, and erythema. There were 14 severe AEs, which included bruising (7 events), swelling (5 events), and pain (2 events). Most events resolved spontaneously within 2 weeks. Of the 103 subjects enrolled, 84% had moderate or significant volume deficiency at baseline. At the first post-treatment evaluation (week 8), 96% were documented as MFVDS responders, with 98% and 100% graded as GAIS responders as assessed by the subjects and investigators, respectively. At week 78, 81.7% of subjects were still MFVDS responders, with 73.2% and 78.1% GAIS responders, respectively.

Table 17 Incidence of Injection Site Reactions (VOL-AP01)

Event	n (%)[1]	n (%)[2]
	Weeks 0 to 8	Weeks 78 to 108
Contusion[3]	42 (40.8)	2 (1.9)
Swelling	15 (14.6)	5 (4.9)
Pain/tenderness	8 (7.8)	1 (1.0)
Erythema	2 (1.9)	0 (0)
Eyelid edema	1 (1.0)	0 (0)
Syncope vasovagal	1 (1.0)	0 (0)

[1]Frequency of adverse events reported during the period: week 0 to 8 in 103 subjects receiving the study treatment at week 0
[2]Frequency of adverse events reported during the period: week 78 to 108 following re-retreatment with the study product in eligible subjects at either week 78 or week 104. Subjects receiving the study treatment at week 104 were followed for a total of 4 weeks post-treatment. New AEs reported between weeks 8 & 78 were documented in the second observational period.
[3]Includes bruising and lump/hematoma

[1] Callan P, Goodman GJ, Carlisle I, Liew S, Muzinkants P et al. Efficacy and safety of a hyaluronic acid filler in subjects treated for correction of midface volume deficiency: a 24 month study. *Clinical, Cosmetic, and Investigational Dermatology.* 2013; 6:81-89

Juvéderm Voluma Post Market Experience: Juvéderm VOLUMA (without lidocaine) received the CE Mark in 2005, and Juvéderm VOLUMA XC received CE mark in 2009. As of December 31, 2012, more than 520,000 syringes of Juvéderm VOLUMA formulations (with and without lidocaine) have been distributed worldwide. Data from post-market surveillance on patient-related and device-related complaints are provided in Table 18. The report rate is the number of events divided by the number of devices distributed.

Table 18 Post Market Medical Events for Juvéderm Voluma

	VOLUMA and VOLUMAXC n[a] = 520,764	
Events[b]	**Number of Events[c]**	**Report Rate**
Swelling/Edema	276	0.0530%
Inflammatory Reaction	265	0.0509%
Nodule	207	0.0397%
Pain	130	0.0250%
Redness/Rash	89	0.0171%
Hematoma/Ecchymosis	50	0.0096%
Loss/Lack of Correction	46	0.0088%
Infection	41	0.0079%
Migration of Product/Displacement	36	0.0069%
Discoloration	31	0.0060%
Granuloma	24	0.0046%
Itching	21	0.0040%
Allergic Reaction/Hypersensitivity	18	0.0035%
Abscess	18	0.0035%
Flu-like Symptoms	17	0.0033%
Necrosis	9	0.0017%
Numbness/Paresthesia	9	0.0017%
Vision Abnormalities	9	0.0017%
Headache	6	0.0012%
Malaise	6	0.0012%

[a] Total syringes sold
[b] Patient-related and device-related complaints for VOLUMA and VOLUMA XC reported at a frequency of 5 or more are listed
[c] Some reports included multiple events, so the above numbers do not indicate the number of complaints nor patients involved

VI Post Approval Study

NOTE TO PANELISTS: FDA's inclusion of a section/discussion on a Post-Approval Study (PAS) in this executive summary should not be interpreted to mean that FDA has made a decision on the approvability of this PMA. The presence of post-approval study plans or commitments does not in any way alter the requirements for premarket approval. A recommendation from the Panel on whether the data demonstrates reasonable assurance on device safety and effectiveness must be based solely on the premarket data. The issues noted below are FDA's comments regarding a potential post-approval study.

The FDA review team has made the recommendation that if Juvéderm Voluma XC is approved, a post-approval study (PAS) should be required as a condition of approval. Through premarket review of the PMA, FDA has identified safety of the device after repeat treatment as a potential postmarket concern and recommends that a PAS be conducted to assess the long-term (12-month) performance of Juvéderm following retreatment.

The sponsor submitted a revised PAS protocol proposal on December 4, 2012. An overview of the proposed PAS protocol is provided below.

Overview of Proposed Post-Approval Study (VOLUMA-003)

Objectives

The objective post-approval study is to evaluate the safety of repeat treatment with Juvéderm Voluma XC in subjects from the premarket pivotal study, VOLUMA-002.

Study Design and Study Population

The data to be included in this statistical analysis protocol are collected in the 12-month follow-up period after repeat treatment in the VOLUMA-002 study.

Hypothesis

Protocol VOLUMA-003 will test the hypothesis that incidence of device-related AEs after repeat treatment will not be more than the incidence rate with a 5% margin for the device-related AEs after initial/touch-up treatment.

Enrollment Plan and Follow-up

Since the proposed PAS is an analytical evaluation of data from the pivotal study, there will be no enrollment of study subjects or clinical sites.

The Month 1 Post Repeat Treatment Follow-up Visit was in-person. The 3, 6, 9, and 12-month Post Repeat Treatment Follow-up visits were an in-person office visit or a telephone/e-mail contact, but not both. If it is an office visit, all applicable safety as well as effectiveness evaluations were performed at that visit. If the contact was via phone/e-mail, only safety evaluations were performed.

Primary Endpoints

Safety will be evaluated by the presence, severity, location (zygomaticomalar region, anteromedial cheek, and/or submalar region), and duration of common treatment site responses (CTRs), and any adverse events (AEs) after repeat treatment during VOLUMA-002. There are no effectiveness analyses planned for this protocol.

Statistical Plan

The VOLUMA-002 study enrolled 235 subjects in the treatment group and 47 subjects in the "no-treatment" control group, for a total of 282 mITT subjects. The 24-month interim Clinical Study Report (CSR) for VOLUMA-002 showed that 125 mITT subjects have received repeat treatment to date, and

these subjects can potentially be included as subjects in this statistical protocol's primary endpoint. As reported in the 24-month CSR, the incidence of device-related AEs after initial/touch-up treatment and prior to repeat treatment for the 125 subjects was 32%. Assuming that the incidence of device-related AEs after repeat treatment will be less than 22%, a sample of 125 subjects provides 93% power using a 1-sided McNemar test at the 5% level to test that the incidence after repeat treatment will not be more than the incidence with a 5% margin after initial/touch-up treatment. The proportion of discordant pairs is assumed to be 29% for sample size calculation.

All safety analyses will be performed on the mITT subjects who received repeat treatment in the VOLUMA-002 study. The presence, severity, location (zygomaticomalar region, anteromedial cheek, and/or submalar region), and duration of CTRs and AEs will be summarized. A 1-sided 95% Unmodified Wald's CI for the difference in the incidence rates of device-related AEs after initial and repeat treatment will be constructed to test the primary safety hypothesis.

FDA Assessment of PAS Proposal

1. *Study Design*

   Analysis of 12-month follow-up data after repeat treatment in VOLUMA-002, the pivotal premarket study, is an acceptable approach that will provide necessary information on the long-term safety of Juvéderm Voluma XC after retreatment.

2. *Enrollment and follow-up*

   Enrollment for VOLUMA-003 is complete, as all patients for this study were enrolled during the pivotal premarket study.

3. *Outcomes*

   The sponsor proposes to assess safety by evaluating the presence, severity, location (zygomaticomalar region, anteromedial cheek, and/or submalar region), and duration of common treatment site responses (CTRs) and any adverse events (AEs) after repeat treatment. These outcomes are appropriate for evaluating the safety of Juvéderm Voluma XC after retreatment.

4. *Statistical plan*

   Data will be summarized descriptively, with categorical and select ordinal variables summarized with frequencies and percentages and continuous variables summarized with mean, median, standard deviation, minimum, and maximum. Where appropriate, 2-sided 95% CIs will be provided as part of the descriptive summary.

   From an epidemiologic perspective the proposed statistical plan is acceptable for the long-term safety evaluation (12-month post retreatment).

VII Addendum

1. FDA questions for Panel Consideration